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Ergovaline-induced vasoconstriction in an isolated bovine lateral saphenous vein bioassay¹

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ABSTRACT: Ergovaline has been proposed as a toxic component of endophyte-infected tall fescue. As many of the symptoms of fescue toxicosis are a result of compromised circulation, the objective of this study was to examine the vasoconstrictive potentials of ergovaline and a more documented ergopeptide, ergotamine, using a bovine, lateral (cranial branch) saphenous vein bioassay. Segments of the cranial branch of the lateral saphenous vein (2 to 3 cm) were collected from healthy, mixed breed cattle (n = 12 and n = 5 for the ergovaline and ergotamine experiments, respectively) at local abattoirs. The veins were trimmed of excess fat and connective tissue, sliced into 2- to 3-mm cross sections, and suspended in a myograph chamber containing 5 mL of a modified Krebs-Henseleit, oxygenated buffer (95% O₂ + 5% CO₂; pH = 7.4; 37°C). The tissue was allowed to equilibrate at 1 g of tension for 90 min before of the addition of treatments. Increasing doses of ergovaline (1 × 10⁻¹¹ to 1 × 10⁻⁴ M) or ergotamine (1 × 10⁻¹¹ to 1 × 10⁻⁵ M) were administered every 15 min after buffer

replacement. Contractile response data were normalized to a percentage induced by a reference dose of norepinephrine (1 × 10⁻⁴ M). Contractile responses of saphenous veins were similar for ergovaline and ergotamine. Initial contractile responses began at 1 × 10⁻⁸ M for both ergovaline and ergotamine (4.4 ± 0.8% and 5.6 ± 1.1%, respectively). Vascular tension continued to increase as the alkaloid concentrations increased (maximums: 43.7 ± 7.1% at 1 × 10⁻⁵ M ergotamine; 69.6 ± 5.3% at 1 × 10⁻⁴ M ergovaline). Interestingly, ergovaline-induced contractions (1 × 10⁻⁴ M) were not reversed by repeated buffer replacement over a 105-min period. As previously shown with ergotamine, these results confirm that ergovaline is a potent vasoconstrictor. The resistance of an ergovaline-induced contraction to relaxation over an extended period of time suggests a potential for bioaccumulation of this ergopeptide alkaloid and may aid in understanding its toxicity within the animal.

Key words: alkaloid, bovine, ergovaline, ergotamine, fescue, vasoconstriction

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INTRODUCTION

Ergovaline has been reported as the most abundant (Yates et al., 1985; Lyons et al., 1986) of the ergopeptide alkaloids produced by the endophyte *Neotyphodium coenophialum* in infected tall fescue [*Schedonorus arundinaceus* (Schreb.) Dumort.; Soreng et al., 2001]. This has led to the perception that ergovaline is a primary

toxicant in the fescue toxicosis syndrome, in which peripheral vasoconstriction is a symptom. Because of its greater commercial availability and use in the treatment of migraines, much of the pharmacologic research into ergot alkaloid action has been conducted using ergotamine, an ergopeptide structurally similar to ergovaline (Figure 1), but produced at much lower levels in endophyte-infected tall fescue (Yates et al., 1985). Ergotamine has been shown to elicit contractile responses in bovine, dorsal pedal vein (Solomons et al., 1989), equine lateral saphenous vein and dorsal metatarsal artery (Abney et al., 1993), and rat tail artery (Schöning et al., 2001). Ergovaline was shown to be a potent vasoconstrictor of bovine uterine and umbilical arteries (Dyer, 1993) and rat ventral caudal and guinea pig iliac arteries (Schöning et al., 2001).

¹Mention of trade name, proprietary product, or specified equipment does not constitute a guarantee or warranty by the USDA and does not imply approval to the exclusion of other products that may be suitable.

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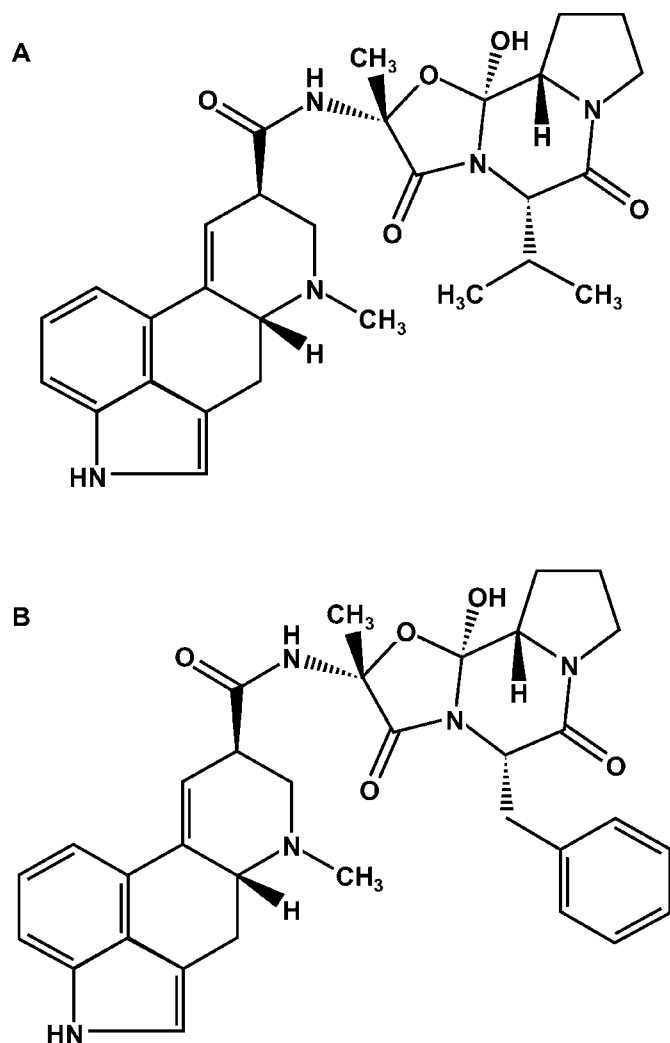


Figure 1. Chemical structures of A) ergovaline and B) ergotamine.

Currently, the effects of ergovaline on bovine peripheral vasculature, or in any bovine venous tissues, have yet to be investigated. Klotz et al. (2006) indicated that the use of a bovine lateral saphenous vein bioassay coupled with the use of a multimyograph was an effective tool to screen for the bioactivity of alkaloids as related to the vascular symptoms of fescue toxicosis. Ergotamine has been previously shown to be bioactive in peripheral bovine vasculature (Solomons et al., 1989); therefore, it was hypothesized that ergovaline would act similarly.

Thus, the objective of the current study was to evaluate the vasoconstrictive effects of increasing concentrations of ergovaline in relation to that of ergotamine using a bovine lateral saphenous vein bioassay and a multimyograph.

MATERIALS AND METHODS

Animals and Tissues

Procedures used in this study did not require approval from the Animal Care and Use Committee be-

cause no live animals were used. The tissues were collected from cattle of mixed breeds and sexes ($n = 17$; BW = 397 ± 28 kg) immediately after slaughter at local abattoirs and were processed according to the methods of Klotz et al. (2006). Briefly, segments (2 to 3 cm in length) of the cranial branch of the lateral saphenous vein were removed (immediately after the division of the lateral saphenous vein into cranial and caudal branches and before the junction of the cranial branch with a branch of the cranial tibial vein) and placed in a modified Krebs-Henseleit, oxygenated buffer solution (95% O_2 + 5% CO_2 ; pH = 7.4; mM composition = D-glucose, 11.1; $MgSO_4$, 1.2; KH_2PO_4 , 1.2; KCl, 4.7; NaCl, 118.1; $CaCl_2$, 3.4; and $NaHCO_3$, 24.9; Sigma Chemical Co., St. Louis, MO) for transport and were kept on ice until processed.

Excess fat and connective tissue were carefully removed from the venous segments, which were then sliced into 2- to 3-mm cross sections. Cross sections were examined under a dissecting microscope (Stemi 2000-C, Carl Zeiss Inc., Oberkochen, Germany) at 12.5 \times magnification to verify the physical integrity of the tissue and to assure that consistent segment size dimensions were measured (Axiovision, version 20, Carl Zeiss Inc.). Duplicate cross sections from each animal were horizontally suspended in a tissue bath (DMT610M Multichamber myograph, Danish Myo Technologies, Atlanta, GA) containing 5 mL of continuously gassed (95% O_2 + 5% CO_2), modified Krebs-Henseleit buffer (37°C). The transport buffer was modified for incubations with the addition of desipramine (3×10^{-5} M; D3900, Sigma Chemical Co.) and propranolol (1×10^{-6} M; P0844, Sigma Chemical Co.) to inactivate neuronal uptake of catecholamines and to block beta-adrenergic receptors, respectively. The tissue segments were allowed to equilibrate under a resting tension of 1 g for 90 min. The buffer solution was replaced at 15-min intervals during the equilibration period. To assure tissue responsiveness, the tissue was exposed to norepinephrine (1×10^{-4} M) and deemed nonviable if the maximal contractile response to norepinephrine was < 10 g. Viable tissues were washed after the norepinephrine treatment every 15 min until the original 1 g of resting tension was reestablished.

Evaluation of Ergotamine and Ergovaline

Stock standards of ergotamine D-tartrate ($\geq 97\%$ purity, #45510, Fluka, as distributed by Sigma Chemical Co.) and ergovaline tartrate ($\geq 93\%$ purity, supplied by F. T. Smith, Auburn University, Auburn, AL) were prepared in 100% (vol/vol) methanol. To achieve a 1×10^{-4} M concentration in the incubation buffer, a 2×10^{-2} M stock concentration was prepared (for ergotamine, the maximum stock concentration that could be made was 2×10^{-3} M, which resulted in a maximum 1×10^{-5} M concentration in the incubation buffer). Serial dilutions of this stock made up the remaining standards, and 25 μ L aliquots of the dilutions were added

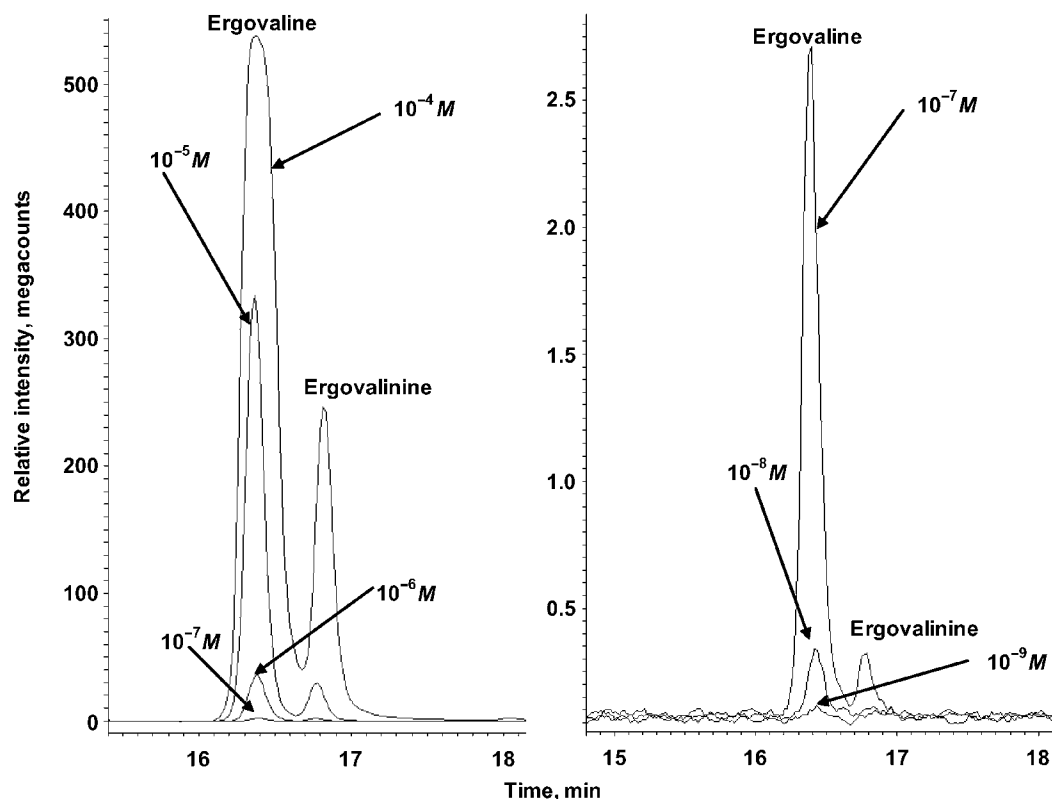


Figure 2. A) Total ion chromatogram for various concentrations (1×10^{-4} to 1×10^{-8} M) of ergovaline in modified, Krebs-Henseleit, incubation buffer as analyzed using high performance liquid chromatography coupled to mass spectrometry. The singly protonated molecular ion for ergovaline ($m/z = 534$) is plotted. B) A magnified view of 1×10^{-7} to 1×10^{-9} M ergovaline illustrates the detection limits for ergovaline.

to the incubation buffer to attain the desired treatment concentrations. Using this protocol, methanol concentrations in the incubation buffer were kept below 0.5%.

Cross sections of the cranial branch of the lateral saphenous vein were run in duplicate from each animal for ergotamine ($n = 5$) and for ergovaline ($n = 12$). After recovery from the norepinephrine viability assessment, the tissues were exposed to increasing concentrations of ergotamine standards (1×10^{-11} to 1×10^{-5} M) or ergovaline standards (1×10^{-11} to 1×10^{-4} M) in 15-min intervals. The 15-min interval consisted of a 9-min incubation period followed by 2 ergopeptide-free buffer changes maintained for 2.5-min each. The buffer was changed a third time, and after a 1-min recovery the next standard was added.

After the initial ergopeptide experiments, it became apparent that a cumulative concentration-response would be required, because the tissue was not relaxing during the buffer changes between treatment additions. To further investigate the stability of ergovaline binding, a single addition of 1×10^{-4} M ergovaline was added and followed by ergopeptide-free buffer replacement every 15 min for a 105-min wash out period. These experiments were conducted alongside the ergovaline and ergotamine concentration-response experiments using segments from saphenous veins collected for those experiments ($n = 9$ cattle).

Liquid Chromatography-Mass Spectrometry of Ergovaline

Relative concentrations of the ergovaline standards used in the incubation buffer were confirmed by HPLC-mass spectrometry using a Varian 1200L quadrupole system equipped with a Varian electrospray source, 2 Varian ProStar solvent delivery modules, and a Varian ProStar 430 autosampler (Varian Inc., Walnut Creek, CA). The samples did not require cleanup or preconcentration before injection. A 10- μ L aliquot of ergovaline-containing incubation buffer with concentrations ranging from 10^{-4} to 10^{-9} M was injected onto a 2-mm reverse phase column (Gemini-RP C18, Phenomenex, Torrance, CA). Each sample was first eluted with 5%/95% acetonitrile/water (both solvents containing 0.1% formic acid) for 1.0 min. A linear gradient then increased the acetonitrile to 50% by 34 min and held at this solvent composition for 6 additional min. The solvent composition was returned to the initial conditions for 9 min to reequilibrate the column for the next sample run. The flow rate for each sample analyzed was 0.2 mL/min. The column eluate was coupled with the electrospray source (ESI; needle set at 5 kV, shield 600 V) to generate positive ions for mass spectrometry analysis (Varian 1200L MS conditions; detector 1400 V, N_2 drying gas 200°C). The 0.1% formic acid in the solvent was present to aid in the

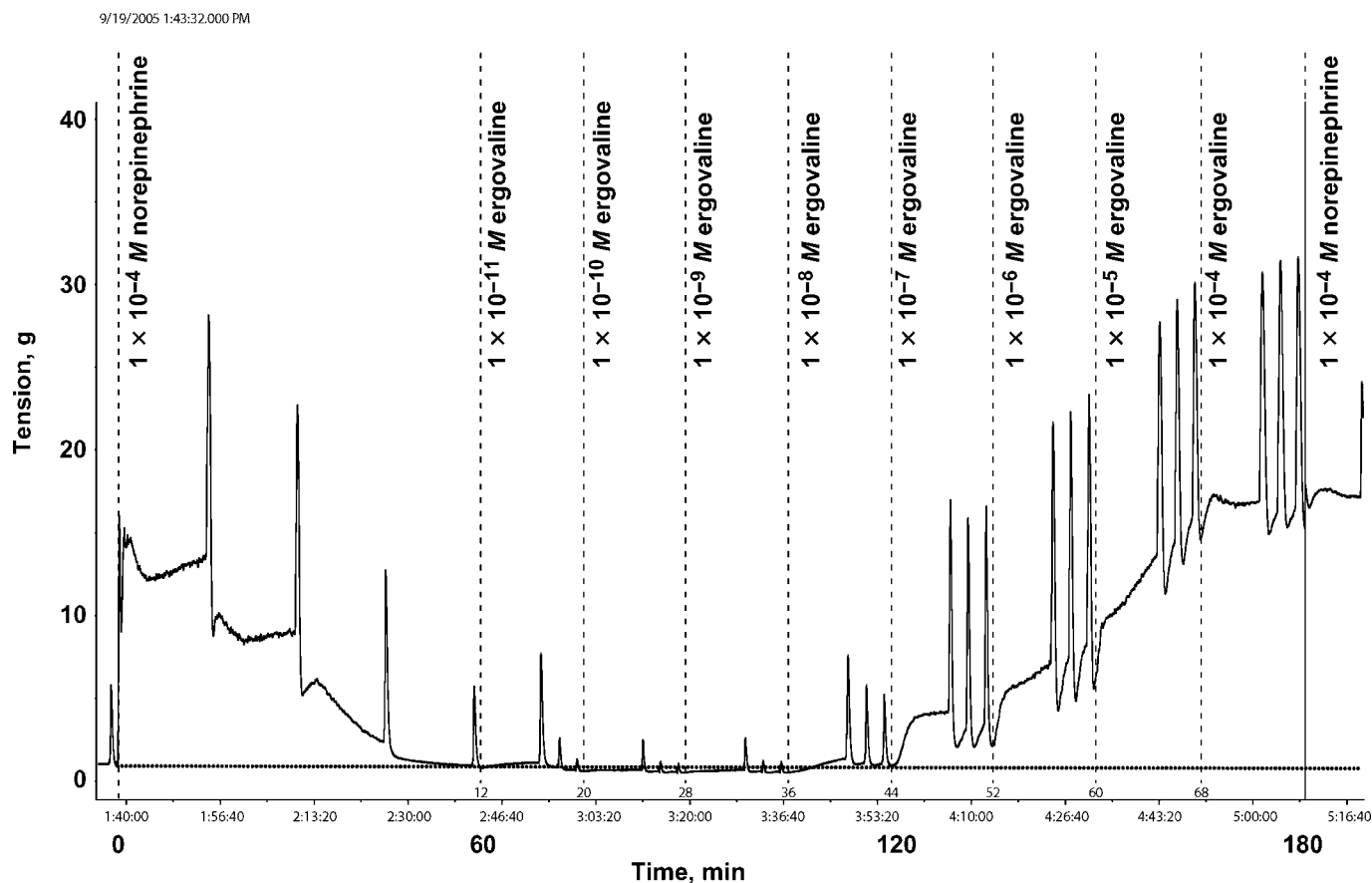


Figure 3. Example of a typical response of isolated, bovine lateral saphenous vein, cross sections to increasing concentrations of ergovaline before correction for baseline tension and normalization. The spikes that precede each addition are artifacts generated from buffer replacement and are not included in the data collection or analysis. This is a complete data recording from 1 channel of the myograph that includes the initial addition of norepinephrine (NE; 1×10^{-4} M), the addition of the ergovaline standards (1×10^{-11} to 1×10^{-4} M), and the concluding addition of NE (1×10^{-4} M).

ionization process. The retention time of the ergovaline was on the order of 16.3 ± 0.1 min. Concentrations referenced throughout the current study are in terms of total ergovaline (the sum of the 2 isomers, ergovaline and ergovalinine).

Data Collection and Analysis

Isometric contractions were recorded as grams of tension in response to exposure to norepinephrine, ergotamine, and ergovaline. The data were digitally recorded using a Powerlab/8sp (ADInstruments, Colorado Springs, CO) and Chart software (Version 5.3, ADInstruments). The contractile response was recorded as the greatest contractile response, in grams, within the 9 min after a treatment addition and corrected by the baseline tension recorded just before the addition of 1×10^{-4} M norepinephrine. The response data were normalized as a percentage of the contraction produced by norepinephrine (1×10^{-4} M). Normalization compensated for variation of the tissue responsiveness due to differences in tissue size or individual cattle. To con-

struct the concentration-response curve for the ergopeptide experiments, the normalized data were averaged within dose and SE were calculated. The mean response and SE were then plotted to illustrate the response of the bovine lateral saphenous vein.

Concentration responses of ergovaline and ergotamine were compared to determine if differences in their effects existed. Data for each alkaloid were analyzed (except for 1×10^{-4} M) as a completely randomized design using JMP (SAS Inst. Inc., Cary, NC). The model included alkaloid, concentration, and the alkaloid \times concentration interaction. Analysis of variance was conducted, and pairwise comparisons of least squares means (\pm SEM) were performed if the probability of a greater *F*-statistic was significant for a tested effect. Comparisons were considered significant at $P \leq 0.05$.

RESULTS AND DISCUSSION

Verification of ergovaline in relative concentrations in the incubation buffer was important to ensure the active form of ergovaline existed in solution (i.e., no

degradation products). The molecular ion of ergovaline was subjected to tandem mass spectrometry with collision-induced dissociation to produce fragmentation. The fragmentation pattern of ergovaline was in agreement with previous reports (Lehner et al., 2004). Another form of ergovaline was determined in the form of the isomer ergovalinine (Figure 2). The isomer has a molecular ion with the same molecular ion weight and fragmentation pattern (after collision-induced dissociation) as ergovaline. It has been shown that epimerization of ergopeptine alkaloids can occur in organic and aqueous solvents similar to those used in the current study (Smith and Shappell, 2002). The identification of ergovalinine was important to ensure the biological activity of the treatments because ergovalinine has been alleged to be biologically inactive (Berde and Stürmer, 1978; Smith and Shappell, 2002). In the current study, the identity and relative concentrations of ergovaline in the incubation buffer were confirmed via HPLC-mass spectrometry for the 1×10^{-4} to 1×10^{-9} M concentrations of ergovaline with a retention time of approximately 16.3 min (Figure 2). The presence of ergovalinine can also be observed with a retention time of 16.8 min (Figure 2). The detection limit for ergovaline was 1×10^{-8} M, as 1×10^{-9} M produced a signal that was indistinguishable from baseline noise.

The tissue segments used in the ergovaline and ergotamine concentration response experiments had average lengths of 2.6 ± 0.1 and 2.9 ± 0.1 , i.d. of 0.8 ± 0.1 and 0.9 ± 0.2 , and o.d. of 3.1 ± 0.1 and 3.4 ± 0.2 mm, respectively. Figure 3 shows a typical trace of a lateral saphenous vein segment exposed to increasing concentrations of ergovaline. Mean maximal contractions induced by the norepinephrine reference dose (1×10^{-4} M) were 22.5 ± 2.4 and 33.0 ± 5.5 g for ergovaline and ergotamine experiments, respectively. Treatment of bovine saphenous veins with increasing concentrations of ergovaline and ergotamine resulted in similar responses, with contractile responses or potencies beginning at 1×10^{-8} M (Figure 4). The greatest contractile intensity observed for the greatest concentration of ergovaline (Figure 4, panel B) was $69.6 \pm 5.3\%$. The contractile intensities did not differ at 1×10^{-5} M for ergovaline and ergotamine at $49.2 \pm 4.7\%$ and $43.7 \pm 7.11\%$, respectively (1×10^{-5} M was the maximum concentration for ergotamine). Moreover, alkaloid and alkaloid \times concentration effects were not significant, but the concentration effect was significant for each alkaloid ($P < 0.001$). Although the 2 ergopeptines differ slightly structurally (Figure 1), there appears to be little difference in the vascular response generated by either. Using a rat tail artery bioassay, Schöning et al. (2001) demonstrated a maximum contractile response at 1×10^{-7} M ergotamine of $52 \pm 4\%$ of the maximum 5-hydroxytryptamine (5-HT or serotonin) response. It is difficult to ascertain whether the difference in potencies is due to the animal of origin, differences in the actual bioassay, or the use of serotonin as the reference compound. This bioassay (Schöning et al., 2001) did find similarities in ergovaline and ergot-

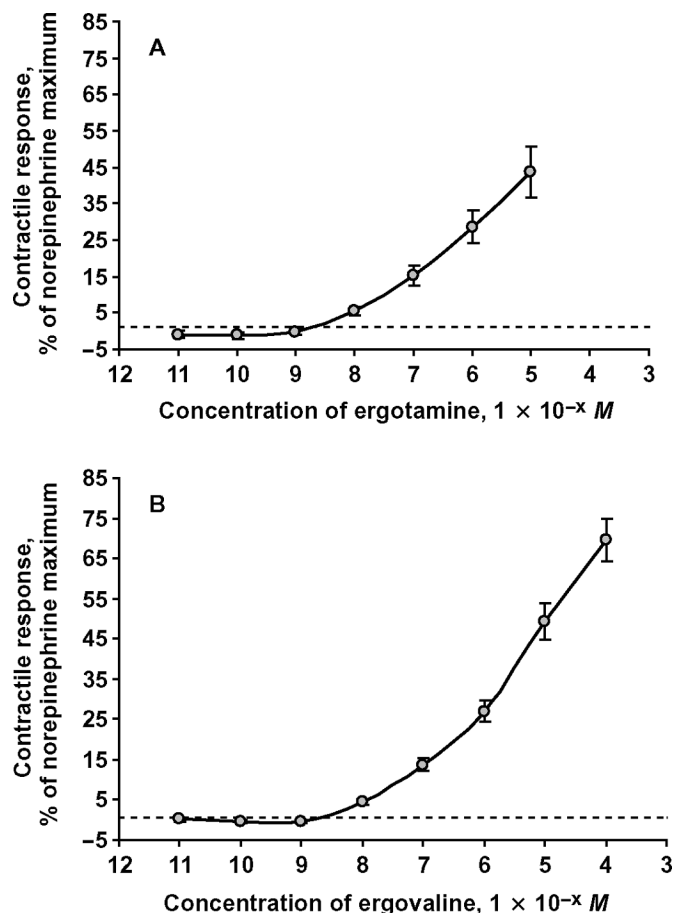


Figure 4. Mean cumulative contractile concentration-response of bovine lateral saphenous veins to A) ergotamine (1×10^{-11} to 1×10^{-5} M; $n = 5$) and B) ergovaline (1×10^{-11} to 1×10^{-4} M; $n = 12$).

amine potency and maximal contractile responses that supported the concentration-responses of the current study.

Solomons et al. (1989) reported a maximal contractile response of 42.9% in bovine dorsal pedal vein segments exposed to 1×10^{-5} M ergotamine, which was similar to that observed in the current study utilizing lateral saphenous veins and ergotamine. Although there are no previous reports addressing vascular contractility induced by ergovaline in the bovine, *in vitro* studies have shown that ergovaline was toxic to dividing bovine vascular smooth muscle cells (Strickland et al., 1996) and dividing Caco-2 cells (Shappell, 2003) and was shown to inhibit synaptosomal Na⁺/K⁺ ATPase activities (Moubarak et al., 1993). Further, intravenous administration of ergovaline has been shown in sheep to decrease the frequency of reticulum and rumen contractions (McLeay and Smith, 2006), as well as cause a decrease in respiratory rate and an increase in blood pressure without a concurrent increase in heart rate (McLeay et al., 2002). Data of the current study coupled to these other reports support ergovaline as a primary toxicant of endophyte-infected tall fescue.

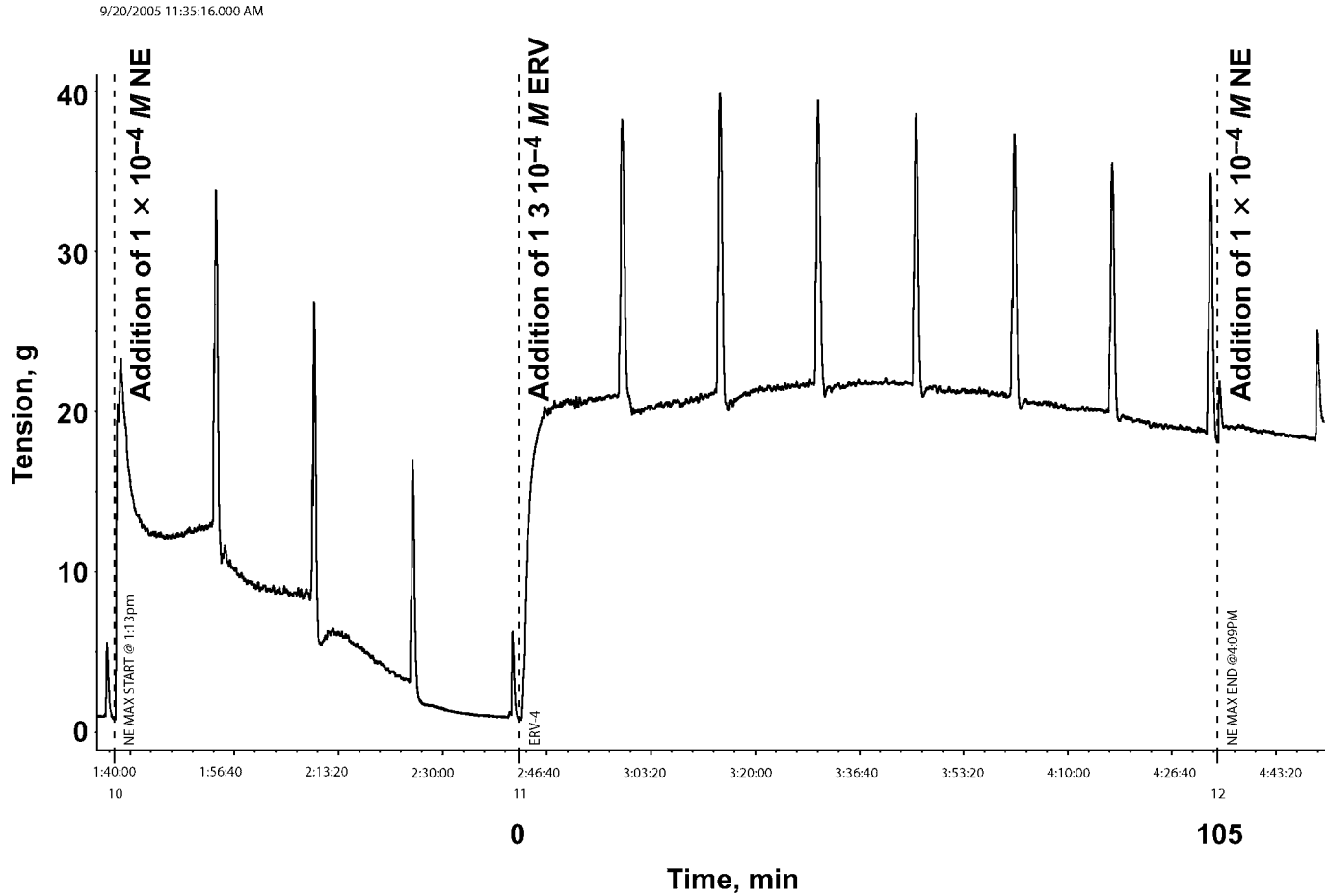


Figure 5. Example of a typical response of isolated bovine lateral saphenous vein, cross sections to a single addition of 1×10^{-4} M ergovaline (ERV) before correction for baseline tension and normalization. Buffer changes occurred every 15 min for a total of 105 min before the concluding addition of norepinephrine (NE).

A noteworthy observation was the longevity of the ergovaline-induced contraction (see Figure 5 for example of the trace/raw data) compared with norepinephrine, which returned to baseline after 3 to 4 buffer changes at 15-min intervals. This experiment was repeated with extra saphenous vein cross sections taken from 9 cattle used in the concentration-response experiments, and the normalized data are presented in Figure 6. After approximately 60 min, the contraction reached the greatest intensity at 99.8% (of the norepinephrine maximum) and then appeared to begin a gradual decline with the 105-min contractile response of 84.5% of the norepinephrine maximum (12.2 ± 3.7 g). This supports observations by Schöning et al. (2001) of an extremely slow dissociation of ergovaline from the 5-HT_{2A} receptor and comparable observation by Solomons et al. (1989) for ergotamine. The findings of these studies strongly suggest the potential for bioaccumulation of ergopeptides, specifically ergovaline and ergotamine, in the animal. This corroborates findings by Schultz et al. (2006) in the evaluation of lysergic acid and ergovaline excretion in geldings that suggested that metabolism or storage of ergovaline occurs.

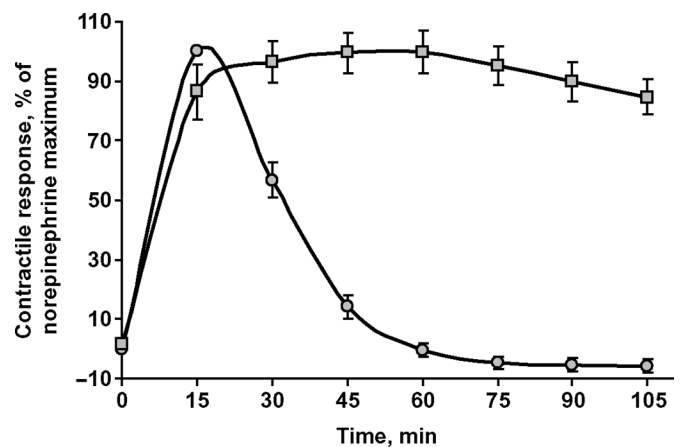


Figure 6. Maintenance of the contractile response of bovine lateral saphenous veins to a single addition (0 min) of 1×10^{-4} M ergovaline (□; $n = 9$) or 1×10^{-4} M norepinephrine (○; $n = 5$). The modified Krebs-Henseleit buffer was replaced every 15 min in both instances.

Results of the current study and the concurrence with the literature suggest that it would take very little ergovaline to result in vasoconstrictive effects that could cause a reduction in peripheral circulation in animals grazing endophyte-infected tall fescue. The potency of 1×10^{-8} M equals approximately 5 ng/mL of ergovaline equivalents in blood. When compared with in vitro absorbance data of ergovaline across Caco-2 cells of 7.5 ng/min/cm² (Shappell and Smith, 2005) and ergotamine movement across sheep foregut epithelia of 7.0 ng/min/cm² (Hill et al., 2001), this vasoconstrictive potency provides further evidence that ergovaline could be directly responsible for vascular toxicity associated with fescue toxicosis.

In conclusion, ergovaline and ergotamine are potent vasoconstrictors, with potencies of 1×10^{-8} M in the bovine lateral saphenous vein bioassay. The concentration responses of ergovaline strongly resembled those of ergotamine. The longevity of the ergovaline-receptor interaction agrees with previous reports using both ergovaline and ergotamine and provides evidence in support of the bioaccumulation hypothesis. The abundance of ergovaline in the plant, the potency, and the binding strength of the alkaloid suggest that it would take only minute quantities (1×10^{-8} M) to elicit a response in the test species and could slowly accumulate over time.

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